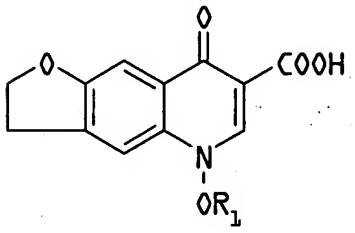
Version with Markings to Show Changes Made

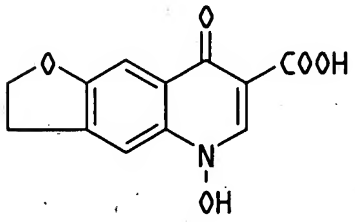
In the Specification

Page 5, paragraph 2 (AMENDED)

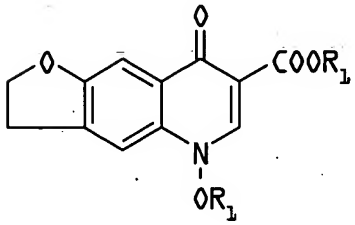
JP-A-49-30369 discloses a method for preparing a quinoline carboxylic acid derivative represented by the formula:



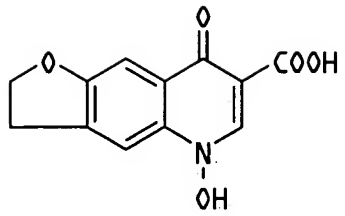
wherein R_1 is a lower alkyl group, which comprises reacting a 1-hydroxy **[group]** -4-quinolone-3-carboxylic acid derivative represented by the formula:



with an alkylating agent to form a quinoline carboxylic acid derivative represented by the formula:



wherein R_1 is as defined above, followed by hydrolyzing, together with a typically exemplified compound represented by the formula:



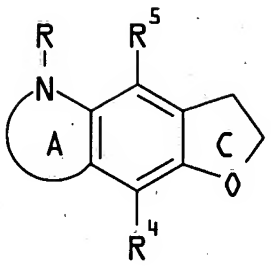
and the like.

Page 7, paragraph 2 (AMENDED)

A lipid peroxidation inhibitor (antioxidant) which has a lipid peroxidation inhibitory activity based on an excellent antioxidative effect and which exhibits an excellent pharmacokinetic profile is expected to exhibit an excellent effect in **[a]** prophylaxis or **[a]** therapy against a central nerve system disease (for example, ischemic central nerve disease (e.g., cerebral infarction, cerebral hemorrhage, cerebral edema), central nerve damage (e.g., cranial trauma, spinal damage, whiplash), neurodegenerative disease (e.g., Alzheimer's disease, **[Perkinson's]** **Parkinson's** disease, Huntington's chorea, amyotrophic lateral sclerosis), vascular dementia (e.g., multi-infarct dementia, Binswanger's disease), **[maniac]** **manic** -depressive, melancholia, schizophrenia, chronic pain, trigeminal neuralgia, migraine and the like), a circulatory system disease or failure (for example, ischemic heart disease (e.g., cardiac infarction, angina **[pectris]** **pectoris**), arterial sclerosis, post-PCTA (percutaneous transluminal coronary angioplasty) arterial restenosis, lower urinary tract disease or failure (e.g., dysuria, urinary incontinence) and the like), **[a]** diabetic neurosis and the like.

Page 10, paragraph 6 (AMENDED)

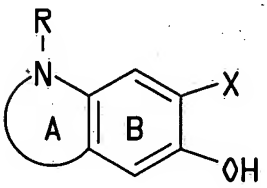
(6) the compound according to the above-mentioned (1) represented by the formula:



wherein R^4 and R^5 are the same or different and each denotes hydrogen atom, a halogen atom, hydroxy group **[group]**, amino group or a hydrocarbon group which may be bonded directly or via oxygen atom, nitrogen atom or sulfur atom and which may be substituted, and the other symbols are as defined above, provided that both R^4 and R^5 are not hydrogen atoms at the same time, or a salt thereof,

Page 13, paragraph 7 (AMENDED)

(18) a method for producing Compound (I) which comprises subjecting a substituent X and hydroxy group **[group]** on Ring B in a compound represented by the formula:



wherein X is an optionally substituted allyl group, and the other symbols are as defined above, or a salt thereof to a ring-closure reaction,

Page 14, paragraph 4 (AMENDED)

(21) a prophylactic and therapeutic agent according to the above-mentioned (20), wherein said neurodegenerative disease is **[Perkinson's]** **Parkinson's** disease or Alzheimer's disease,

Please substitute the following paragraph for the second paragraph on page 22 of the specification.

Page 22, paragraph 2 (AMENDED)

Examples of the "aromatic heterocyclic group" include a 5- or 6-membered aromatic monocyclic heterocyclic group such as furyl, thienyl, pyrrolyl, oxazolyl, isooxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, etc., a 8- to 12-membered aromatic fused heterocyclic group such as benzofuranyl, isobenzofuranyl, benzothienyl, indolyl, isoindolyl, 1H-indazolyl, benzindazolyl, benzoxazolyl, 1,2-benzoisoxazolyl, benzothiazolyl, 1,2-benzoisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthylidinyl, purinyl, **[puteridinyl]** **pteridinyl**, carbazolyl, α-carbolinyl, β-carbolinyl, γ-carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, **[phenoxathiynyl]** **phenoxthinyl**, thianthrenyl, phenathridinyl, phenathrolinyl, indolidinyl, pyrrolo[1,2-b]pyridazinyl, pyrrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl, 1,2,4-triazolo[4,3-b]pyridazinyl, 1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl, etc. (preferably, a heterocyclic ring formed by a condensation of a 5- to 6-membered aromatic monocyclic heterocyclic group described above with benzene ring, or a heterocyclic ring formed by a condensation of two **of** the same or different heterocyclic rings of 5- to 6-membered aromatic monocyclic heterocyclic groups described above), and the like.

Page 23, paragraph 2 (AMENDED)

Examples of the "non-aromatic heterocyclic group" include a 3- to 8-membered (preferred 5- to 6-membered) saturated or unsaturated (preferably saturated) non-aromatic heterocyclic group such as oxiranyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, **[thioranyl]** **thiolanyl**, piperidyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, piperazinyl, etc., and the like.

Page 23, paragraph 3 (AMENDED)

Examples of the "substituent" which may be possessed by said "heterocyclic group" include (1) an optionally substituted alkyl group, (2) an optionally substituted amino group, (3) an optionally substituted aryl group, (4) an optionally substituted cycloalkenyl group, (5) an optionally substituted cycloalkyl group, (6) an optionally substituted alkenyl group, (7) an optionally substituted alkynyl group, (8) an optionally substituted amidino group, (9) an optionally substituted hydroxy group **[group]**, (10) an optionally substituted thiol group, (11) an optionally esterified carboxyl group, (12) an optionally substituted carbamoyl group, (13) an optionally substituted thiocarbamoyl group, (14) an acyl group, (15) a halogen atom (for example, fluorine, chlorine, bromine, iodine, etc., preferably chlorine, bromine, etc.), (16) cyano group, (17) nitro group, etc., each of which may occur 1 to 5 times (preferably 1 to 3 times) in any substitutable positions.

Page 26, paragraph 4 (AMENDED)

Examples of the substituent on "(2) amino group", "(8) amidino group", "(9) hydroxy **[groupl]** group" and "(10) thiol group" as the substituent include a lower alkyl group (for example, a C_{1-6} alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, etc., or the like), an acyl group (a C_{1-6} alkanoyl group (e.g., formyl, acetyl, propionyl, pivaloyl, etc.), benzoyl, or the like), an optionally halogenated C_{1-6} alkoxy-carbonyl (for example, trifluoromethoxycarbonyl, 2,2,2-trifluoroethoxycarbonyl, trichloromethoxycarbonyl and 2,2,2-trichloroethoxycarbonyl, etc.) and the like, and any of these substituents may be further substituted with an aryl group (for example, a C_{6-10} aryl group such as phenyl, 1-naphthyl, 2-naphthyl, etc., or the like), a heterocyclic group, and the like. Examples of the "heterocyclic group" include the same group as the "heterocyclic group" in "optionally substituted heterocyclic group" described above. Further, "(2) amino group" as the substituent may sometimes form a cyclic amino group when two substituents are taken together with nitrogen atom, and in such case, examples of the cyclic amino group include a 3- to 8-membered (preferably 5- to 6-membered) cyclic amino group such as 1-azetidinyl, 1-pyrrolidinyl, piperidino, morpholino, 1-piperazinyl as well as 1-piperazinyl which may have in its 4-position a lower alkyl group (for example a C_{1-6} alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, pentyl, hexyl, etc., or the like), an aralkyl group (for example a C_{7-10} aralkyl group such as benzyl, phenethyl, etc., or the like), an aryl group (for example a C_{6-10} aryl group such as phenyl, 1-naphthyl, 2-naphthyl, etc., or the like), and the like.

Page 28, paragraph 2 (AMENDED)

Examples of "(11) optionally esterified carboxyl group" include, in **[additiinto]** **addition to** free carboxyl group, a lower alkoxycarbonyl group, an aryloxycarbonyl group, an aralkyloxycarbonyl group and the like.

Page 28, paragraph 4 (AMENDED)

Examples of the "aryloxycarbonyl group" include a C_{7-12} aryloxy-carbonyl group such as phenoxycarbonyl, 1- **[naphthoxycarbpnyl]** **naphthoxycarbonyl**, 2-naphthoxycarbonyl, etc., and the like.

Page 29, paragraph 2 (AMENDED)

Examples of "(12) optionally substituted carbamoyl group" include, in **[additiinto a]** **addition to an** unsubstituted carbamoyl, an N-monosubstituted carbamoyl group and an N,N-disubstituted carbamoyl group.

Page 31, paragraph 5 (AMENDED)

Examples of "cyclic amino group" in the "optionally substituted cyclic amino group" include a 3- to 6-membered cyclic amino group which may contain 1 to 3 heteroatoms selected from oxygen, sulfur and nitrogen atoms in **[additiinto]** **addition to** carbon atoms and one nitrogen atom (for example, a 3- to 6-membered cyclic amino group such as aziridinyl, azetidinyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, imidazolyl, pyrazolyl, imidazolidinyl, piperidino, morpholino, thiomorpholino, dihydropyridyl, pyridyl, N-methylpiperazinyl, N-ethylpiperazinyl, etc.) and the like.

Page 34, paragraph 2 (AMENDED)

Examples of the "non-aromatic 5-to 7-membered nitrogen-containing heterocyclic group" represented by Ring A include a non-aromatic 5- to 7-membered (preferably 5- or 6-membered) nitrogen-containing heterocyclic ring containing at least one nitrogen atom in **[additiinto]** **addition to** carbon atoms, and the like. Specific examples thereof include 2,3-dihydro-1H-

pyrrole, 1,2-dihydropyridine, 1,2,3,4-tetrahydropyridine, 2,3,4,5-tetrahydro-1H-azepine, 2,3-dihydro-1H-azepine and the like.

Page 34, paragraph 3 (AMENDED)

Examples of the substituent which may be further possessed by the "non-aromatic 5- to 7-membered nitrogen-containing heterocyclic ring" include an optionally substituted hydrocarbon group, an optionally halogenated lower alkoxy group, an optionally **[be]** halogenated lower alkylthio group, a halogen atom (for example, fluorine, chlorine, bromine, iodine, etc.), an aryloxy group (for example, a C_{6-10} aryloxy such as phenoxy, etc., or the like), a lower alkanoyl (for example, a C_{1-6} alkyl-carbonyl such as acetyl, propionyl, butyryl, isobutyryl, etc., or the like), an arylcarbonyl group (for example, a C_{6-10} aryl-carbonyl such as benzoyl, naphthoyl, etc.), a lower alkanoyloxy group (for example, a C_{1-6} alkyl-carbonyloxy such as acetyloxy, propionyloxy, butyryloxy, isobutyryloxy, etc., or the like), an arylcarbonyloxy group (for example, a C_{6-10} aryl-carbonyloxy such as benzoyloxy, naphthoyloxy, etc., or the like), carboxyl group, a lower alkoxycarbonyl group (for example, a C_{1-6} alkoxy-carbonyl such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl, etc., or the like), carbamoyl group, thiocarbamoyl group, a mono-lower alkylcarbamoyl group (for example, a mono-C_{1-6} alkyl-carbamoyl such as methylcarbamoyl, ethylcarbamoyl, etc., or the like), a di-lower alkylcarbamoyl (for example, a di-C_{1-6} alkyl-carbamoyl such as dimethylcarbamoyl, diethylcarbamoyl, etc., or the like), a C_{6-10} aryl-carbamoyl (for example, phenylcarbamoyl, naphthylcarbamoyl, etc.), amidino group, imino group, amino group, a mono-lower alkylamino group (for example, a mono-C_{1-6} alkylamino such as methylamino, ethylamino, propylamino, isopropylamino, butylamino, etc., or the like), a di-lower alkylamino group (for example, a di-C_{1-6} **[alkylamiono]** **<u>alkylamino</u>** such as dimethylamino, diethylamino, ethylmethylamino, dipropylamino, diisopropylamino,

dibutylamino, etc., or the like), a 3- to 6-membered cyclic amino group which may contain 1 to 3 heteroatoms selected from oxygen, sulfur and nitrogen atoms in **[additiinto]** **addition to** carbon atoms and one nitrogen atom (for example, a 3- to 6-membered cyclic amino group such as aziridinyl, azetidinyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, imidazolyl, pyrazolyl, imidazolidinyl, piperidino, morpholino, thiomorpholino, dihydropyridyl, pyridyl, N-methylpiperazinyl, N-ethylpiperazinyl, etc., or the like), an alkylenedioxy group (for example, a C_{1-3} alkylenedioxy group such as methylenedioxy, ethylenedioxy, etc., or the like), hydroxy group **[group]**, nitro group, cyano group, mercapto group, sulfo group, sulfino group, phosphono group, sulfamoyl group, a mono-lower alkylsulfamoyl group (for example, a mono-C_{1-6} alkylsulfamoyl group such as methylsulfamoyl, ethylsulfamoyl, propylsulfamoyl, isopropylsulfamoyl, butylsulfamoyl, etc., or the like), a di-lower alkylsulfamoyl group (for example, a di-C_{1-6} alkylsulfamoyl such as dimethylsulfamoyl, diethylsulfamoyl, dipropylsulfamoyl, dibutylsulfamoyl, etc., or the like), an arylthio group (for example, a C_{6-10} arylthio such as phenylthio, naphthylthio, etc., or the like), a lower alkylsulfinyl group (for example, a C_{1-6} alkylsulfinyl such as methylsulfinyl, ethylsulfinyl, propylsulfinyl, butylsulfinyl, etc., or the like), an arylsulfinyl (for example, a C_{6-10} arylsulfinyl such as phenylsulfinyl, naphthylsulfinyl, etc., or the like), a lower alkylsulfonyl group (for example, a C_{1-6} alkylsulfonyl such as methylsulfonyl, ethylsulfonyl, propylsulfonyl, butylsulfonyl, etc., or the like), an arylsulfonyl group (for example, a C_{6-10} arylsulfonyl such as phenylsulfonyl, naphthylsulfonyl, etc., or the like) and the like. When the substituent is an alkylenedioxy group, it preferably forms a ring together with two adjacent carbon atoms.

Page 38, paragraph 3 (AMENDED)

Examples of the substituent which may be possessed by "benzene ring" include a halogen atom (for example, fluorine, chlorine, bromine, iodine, etc.), hydroxy group **[group]**, amino

group or a hydrocarbon group which may be bonded directly or via oxygen atom, nitrogen atom or sulfur atom and which may be substituted.

Page 41, paragraph 4 (AMENDED)

Such substituents on Ring B are preferably a halogen atom or an electron donor (hydroxy group **[group]**, amino group or a hydrocarbon group which may be bonded directly or via oxygen atom, nitrogen atom or sulfur atom and which may be substituted and the like) in view of the action and the efficacy (lipid peroxidation inhibitory activity).

Page 43, paragraph 4 (AMENDED)

Examples of the "aromatic heterocyclic group" include a 5- to 10-membered monocyclic aromatic heterocyclic group or a fused group thereof containing one or more (for example 1 to 4) heteroatoms selected from nitrogen, sulfur and oxygen atoms in **[additiinto]** **addition to** carbon atoms, and the like. Specific examples thereof include an aromatic heterocyclic ring such as thiophene, benzothiophene, benzofuran, benzimidazole, benzoxazole, benzothiazole, benzisothiazole, naphtho[2,3-b]thiophene, furan, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indole, isoindole, 1H-indazole, isoquinoline, quinoline, carbazole, isothiazole and isoxazole, etc., or a monovalent group formed by removing any hydrogen atom from a ring formed by condensation of any of the above rings (preferably a 5- or 6-membered monocyclic ring) with one or more (preferably 1 or 2, more preferably 1) aromatic **[ring]** **rings** (e.g., benzene ring, pyridine ring, etc.), and the like. Preferred examples of "aromatic heterocyclic group" include 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 8-quinolyl, 1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 5-isoquinolyl, 1-indolyl, 2-indolyl, 3-indolyl, 2-benzothiazolyl, 2-benzothienyl, benzofuranyl, 2-thienyl, 3-thienyl, 2-benzooxazolyl, 2-benzimidazolyl, 2-pyridothiazolyl, etc. More preferably, it is 2-

pyridyl, 3-pyridyl, 4-pyridyl, 2- **[qionolyl] quinolyl**, 3-quinolyl, 4-quinolyl, 2-indolyl, 3-indolyl, or the like.

Page 44, paragraph 2 (AMENDED)

Examples of the "substituent" on "optionally substituted aromatic group" represented by Zc include a halogen atom (e.g., fluorine, chlorine, bromine, iodine, etc.), a C_{1-3} alkylenedioxy (e.g., methylenedioxy, ethylenedioxy, etc.), nitro, cyano, an optionally halogenated C_{1-6} alkyl, a C_{3-5} cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.), an optionally halogenated C_{1-6} alkoxy, an optionally halogenated C_{1-6} alkylthio, hydroxy group, amino, a mono-C_{1-6} alkylamino (e.g., methylamino, ethylamino, propylamino, isopropylamino, butylamino, etc.), a di-C_{1-6} alkylamino (e.g., dimethylamino, diethylamino, ethylmethylamino, dipropylamino, dibutylamino, etc.), a C_{1-6} alkyl-carbonyl (e.g., acetyl, **[propiony] propionyl**, etc.), carboxyl, a C_{1-6} alkoxy-carbonyl (e.g., **[methoxy, carbonyl] methoxycarbonyl**, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, etc.), carbamoyl, a mono-C_{1-6} alkyl-carbonyl (e.g., methylcarbamoyl, ethylcarbamoyl, etc.), a di-C_{1-6} alkyl-carbamoyl (e.g., dimethylcarbamoyl, diethylcarbamoyl, etc.), a C_{6-10} arylcarbamoyl (e.g., phenylcarbamoyl, naphthylcarbamoyl, etc.), sulfo, a C_{1-6} alkylsulfonyl (e.g., methylsulfonyl, ethylsulfonyl, etc.), a C_{6-10} aryl (e.g., phenyl, naphthyl, etc.), a C_{6-10} aryloxy (e.g., phenyloxy, naphthyloxy, etc.) and the like. When the substituent is a C_{1-3} alkylenedioxy, it preferably forms a ring together with two adjacent carbon atoms.

Page 47, paragraph 4 (AMENDED)

Examples of the "5- to 8-membered nitrogen-containing heterocyclic ring" in "5- to 8-membered nitrogen-containing heterocyclic ring which may be

substituted and which may be fused with benzene ring" represented by Ring D include a 5- to 8-membered saturated or unsaturated heterocyclic ring containing at least one nitrogen atom in **[additiinto]** **addition to** carbon atoms, and the like. Specific examples thereof include piperidine, piperazine, 1,2,5,6-tetrahydropyridine, pyrrolidine, 1H-azepine, 1H-2,3-dihydroazepine, 1H-2,3,4,5-tetrahydroazepine, 1H-2,3,6,7-tetrahydroazepine, 1H-2,3,4,5,6,7-hexahydroazepine, 1H-1,4-diazepine, 1H-2,3-dihydro-1,4-diazepine, 1H-2,3,4,5-tetrahydro-1,4-diazepine, 1H-2,3,6,7-tetrahydro-1,4-diazepine, 1H-2,3,4,5,6,7-hexahydro-1,4-diazepine, 1,2-dihydroazocine, 2,3,4,5-tetrahydroazocine, 1,2,3,4,5,6-hexahydroazocine, 1,2,3,4,5,6,7,8-octahydroazocine, 1,2-dihydro-1,5-diazocine, 1,2,3,4,5,6-hexahydro-1,5-diazocine, 1,2,3,4,5,6,7,8-octahydro-1,5-diazocine, and the like. Among them, a 6-membered heterocyclic ring is preferred. Those preferred especially include piperidine, piperazine, etc.

Page 51, paragraph 4 (AMENDED)

Specific **[example]** **examples** thereof include:

(i) a C_{1-8} alkylene (e.g., $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$, $-(CH_2)_7-$, $-(CH_2)_8-$, etc.),

(ii) a C_{2-8} alkenylene (e.g., $-CH=CH-$, $-CH_2-CH=CH-$, $-CH_2-CH=CH-CH_2-$, $-CH_2-CH_2-CH=CH-$, $-CH=CH-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-CH_2-CH=CH-$, etc.),

(iii) a C_{2-8} alkynylene (e.g., $-C\equiv C-$, $-CH_2-C\equiv CH-$, $-CH_2-C\equiv C-CH_2-CH_2-$, etc.),

(iv) a group represented by the formula: $-(CH_2)_p-M-(CH_2)_q-$ wherein each of p and q is an integer of 1 to 8, and p+q is an integer of 1 to 8, M is O, NR^{11}, S, SO or SO_2, and the like. In the formula, R^{11} is hydrogen atom, a C_{1-6} alkyl (for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, etc.), a C_{3-6} cycloalkyl (for example, cyclopropyl, cyclobutyl, cyclopentyl, etc.), a C_{6-14} aryl (for example, phenyl, **[1-naphtyl, 2-naphtyl,]** **1-naphthyl, 2-**

naphthyl, biphenylyl, etc.), a C_{7-11} aralkyl (for example, benzyl, phenethyl, etc.), or an acyl. Examples of the "acyl" include the same acyl as that described above.

Page 52, paragraph 4 (AMENDED)

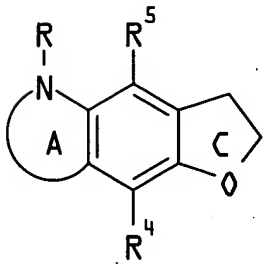
Examples of the "substituent" which may be possessed by said "divalent aliphatic hydrocarbon group which may be bonded directly or via oxygen atom, nitrogen atom or sulfur atom" include a halogen atom (for example, fluorine, chlorine, bromine, iodine, etc.), nitro, cyano, an optionally halogenated C_{1-6} alkyl, a C_{3-6} cycloalkyl (for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.), an optionally halogenated C_{1-6} alkoxy, an optionally halogenated C_{1-6} alkylthio, hydroxy group, amino, mono-C_{1-6} alkylamino (for example, methylamino, ethylamino, propylamino, isopropylamino, butylamino, etc.), a d-C_{1-6} alkylamino (for example, dimethylamino, diethylamino, ethylmethylamino, dipropylamino, dibutylamino, etc.), an optionally substituted C_{6-14} aryl (for example, phenyl, **[1-naphtyl]** **1-naphthyl,** 2-naphthyl, biphenylyl, etc.), an optionally substituted C_{7-11} aralkyl (for example, benzyl, phenethyl, etc.), an optionally substituted C_{6-10} aryloxy (for example, phenyloxy, naphthyloxy, etc.), oxo, an acyl, and the like. Examples of the "optionally halogenated C_{1-6} alkyl", "optionally halogenated C_{1-6} alkoxy" and "optionally halogenated C_{1-6} alkylthio" described above include the same groups as those detailed with regard to the substituent on aromatic group represented by Zc described above. Examples the "substituent" on "optionally substituted C_{6-14} aryl", "optionally substituted C_{7-11} aralkyl" and "optionally substituted C_{6-10} aryloxy" described above include the same group as the "substituent" which may be possessed by "hydrocarbon group" in "optionally substituted hydrocarbon group" described above. The "acyl" described above may for example be the same "acyl" as that described above.

Page 54, paragraph 7 (AMENDED)

R is preferably hydrogen atom, formyl or a C_{1-6} alkyl-carbonyl or C_{6-10} aryl-carbonyl optionally substituted with **[haloten]** **halogen** atom(s).

Page 54, paragraph 8 (AMENDED)

As Compound (I), a compound represented by the formula:



wherein R^4 and R^5 are the same or different and each denotes hydrogen atom, a halogen atom, hydroxy **[group]** group, amino group or a hydrocarbon group which may be bonded directly or via oxygen atom, nitrogen atom or sulfur atom and which may be substituted, and the other symbols are as defined above, provided that both R^4 and R^5 are not hydrogen atoms at the same time, or a salt thereof is preferred.

Page 65, paragraph 2 (AMENDED)

This reaction is conducted advantageously by using a solvent which is inert to the reaction. Such solvent is not limited particularly provided that it allows the **[reactiinto be proceeded]** **reaction to proceed**, and may for example be an alcohol, an ether, an aliphatic hydrocarbon, an aromatic hydrocarbon, an amide, a halogenated hydrocarbon, a nitrile and a sulfoxide as well as a mixture thereof.

Page 66, paragraph 4 (AMENDED)

This reaction is conducted advantageously by using a solvent which is inert to the reaction. Such solvent is not limited particularly provided that it allows the **[reactiinto be proceeded]** **reaction to proceed**, and may for example be an ether, an aliphatic hydrocarbon, an aromatic hydrocarbon, an amide, a halogenated hydrocarbon, a nitrile and a sulfoxide as well as a mixture thereof.

Page 66, paragraph 7 (AMENDED)

This reaction is conducted without any solvent, or may advantageously be conducted using a solvent which is inert to the reaction. Such solvent is not limited particularly provided that it allows the **[reactiinto be proceeded]** **reaction to proceed**, and may for example be an alcohol, an aliphatic hydrocarbon, an aromatic hydrocarbon, an organic acid, an ether, an aniline and a halogenated hydrocarbon as well as a mixture thereof.

Page 67, paragraph 4 (AMENDED)

Compound (Ia) can be prepared by subjecting Compound (V) to a ring closure in the presence of a protonic acid or a Lewis acid. A protonic acid may for example be a mineral acid such as hydrochloric acid, hydrobromic acid and sulfuric acid and a sulfonic acid such as trifluoromethanesulfonic acid and fluorosulfonic acid, while a Lewis acid may for example be aluminum chloride, aluminum bromide, titanium tetrachloride, tin (IV) chloride, zinc chloride, boron trichloride, boron tribromide and boron trifluoride. While each of a protonic acid and a Lewis acid is usually employed alone, **[it]** **they** may be combined with each other if necessary. A protic acid is employed usually in an amount of about 1.0 to about 200 moles, preferably about 1.0 to about 100 moles per mole of Compound (V). A Lewis acid is employed usually in

an amount of about 1.0 to about 5.0 moles, preferably about 1.0 to about 3.0 moles per mole of Compound (V). This reaction is conducted advantageously by using a solvent which is inert to the reaction. Such solvent is not limited particularly provided that it allows the **[reactiinto be proceeded]** **reaction to proceed**, and may for example be an ether, an aliphatic hydrocarbon, an aromatic hydrocarbon, an amide, a halogenated hydrocarbon, a nitrile and a sulfoxide as well as a mixture thereof. The reaction temperature is usually about -20 to about 150°C, preferably about 0 to about 100°C. The reaction time ranges usually from about 5 minutes to about 24 hours, preferably about 10 minutes to about 5 hours. While a product still in a solution or as a crude product may be used in the next reaction, it can be isolated from a reaction mixture by an ordinary method, and can readily be purified by a separating procedure such as recrystallization, distillation, chromatography or the like.

Page 69, paragraph 3 (AMENDED)

The "halogenating reagent" may for example be a halogen such as bromine, chlorine, iodine, or the like, an imide such as N- **[bromosuccineimide]** **bromosuccinimide**, or the like, a halogen adduct such as benzyltrimethylammonium dichloroiodate, benzyltrimethylammonium tribromide, etc., or the like. The halogenating reagent is employed in an amount of about 1 to about 5 moles, preferably about 1 to about 2 moles per mole of Compound (V).

Page 69, paragraph 4 (AMENDED)

This reaction may advantageously be conducted using a solvent which is inert to the reaction. Such solvent is not limited particularly provided that it allows the **[reactiinto be proceeded]** **reaction to proceed**, and may for example be an alcohol, an aliphatic hydrocarbon,

an aromatic hydrocarbon, an amide, a halogenated hydrocarbon, a nitrile, a sulfoxide, an organic acid, a nitroalkane and an aromatic amine as well as a mixture thereof.

Page 71, paragraph 4 (AMENDED)

The organic peracid may for example be m-chloroperbenzoic acid, peracetic acid, etc. The organic peracid is employed in an amount of about 1.0 to about 5.0 moles, preferably about 1.0 to about 2.0 moles, per mole of Compound (V)[,]. This reaction may advantageously be conducted using a solvent which is inert to the reaction. Such solvent is not limited particularly provided that it allows the **[reactiinto be proceeded]** **reaction to proceed**, and may for example be water, an ether, an aliphatic hydrocarbon, an aromatic hydrocarbon, an amide, a halogenated hydrocarbon, a nitrile, a sulfoxide, an organic acid and an aromatic amine as well as a mixture thereof. The base employed if necessary may for example be a basic salt such as sodium carbonate, potassium carbonate, cesium carbonate, calcium carbonate and sodium hydrogen carbonate, an aromatic amine such as pyridine and lutidine, a tertiary amine such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine and N-methylmorpholine. The reaction temperature is usually about -20 to about 150°C, preferably about 0 to about 100°C. The reaction time ranges usually from about 5 minutes to about 24 hours, preferably about 10 minutes to about 5 hours. Product (Ia) can be isolated from a reaction mixture by an ordinary method, and can readily be purified by a separating procedure such as recrystallization, distillation, chromatography, etc.

Page 74, paragraph 4 (AMENDED)

This reaction is conducted advantageously by using a solvent which is inert to the reaction. Such solvent is not limited particularly provided that it allows the **[reactiinto be proceeded]** **reaction to proceed**, and may for example be an alcohol, an ether, an aliphatic hydrocarbon, an aromatic hydrocarbon, an amide, a halogenated hydrocarbon, a nitrile and a sulfoxide as well as a mixture thereof.

Page 76, paragraph 1 (AMENDED)

This reaction is conducted advantageously by using a solvent which is inert to the reaction. Such solvent is not limited particularly provided that it allows the **[reactiinto be proceeded]** **reaction to proceed**, and may for example be an ether, an aliphatic hydrocarbon, an aromatic hydrocarbon, an amide, a halogenated hydrocarbon, a nitrile and a sulfoxide as well as a mixture thereof.

Page 77, paragraph 4 (AMENDED)

A 2,3-dihydro-5- **[hydroxy groupindole]** **hydroxyindole** derivative employed in Synthesis Method 1 is produced by a process shown in Synthesis Methods 3-1, 3-2 and 3-3.

Page 78, paragraph 1 (AMENDED)

Compound (XIII) is prepared by reducing Compound (XII). A reducing agent may for example be sodium hydrosulfite and tin (II) chloride. The amount of a reducing agent per mole of Compound (XII) is, for example, about 1.0 to about 30 moles, preferably about 2.0 to about

5.0 moles when sodium hydrosulfite is employed, while it is about 1.0 to about 10 moles, preferably about 2.0 to about 5.0 moles when tin (II) chloride is employed. When tin (II) chloride is employed as a reducing agent, it is reacted under an acidic condition usually in the presence of a mineral acid such as hydrochloric acid. This reaction is conducted advantageously by using a solvent which is inert to the reaction. Such solvent is not limited particularly provided that it allows the **[reactiinto be proceeded]** **reaction to proceed**, and may for example be water, or a mixture of water with an alcohol, an ether, an aliphatic hydrocarbon, an aromatic hydrocarbon and an amide. The reaction time ranges usually from about 10 minutes to about 10 hours, preferably about 10 minutes to about 2 hours. The reaction temperature is usually about 0 to about 100°C, preferably about 5 to about 80°C. While a product still in a solution or as a crude product may be used in the next reaction, it can be isolated from a reaction mixture by an ordinary method, and can readily be purified by a separating procedure such as recrystallization, distillation, chromatography, or the like.

Page 95, paragraph 1 (AMENDED)

Compound (XXII) is prepared from Compound (XX) via Compound (XXI) by a selective hydroxy **[grouplmethylation in]** **methylation at** the ortho-position **[in]** **of the** phenol.

Page 95, paragraph 2 (AMENDED)

Compound (XXI) is produced by reacting Compound (XX) with phenylboronic acid and p-formaldehyde in the presence of an acid with **[removing]** **removal of** any generated water using for example a **[Deen]** **Dean** -Stark trap. Phenylboronic acid is employed in an amount of about 1.0 to about 10 moles, preferably about 1.0 to about 1.5 moles per mole of Compound (XX). Paraformaldehyde is employed in an amount of about 1.0 to about 30 moles, preferably

about 3 to about 5 moles per mole of Compound (XX). An acid catalyst may for example be an organic acid such as acetic acid, propionic acid and trichloroacetic acid which is used in an amount of about 0.01 to about 10 moles, preferably about 0.1 to about 0.5 moles per mole of Compound (XX). This reaction is conducted advantageously by using a solvent which is inert to the reaction. Such solvent is not limited particularly provided that it allows the **[reactiinto be proceeded]** **reaction to proceed**, and may for example be an ether, an aliphatic hydrocarbon and an aromatic hydrocarbon as well as a mixture thereof, preferably benzene and toluene. The reaction temperature is usually about 0 to about 200°C, preferably about 50 to about 150°C. While the reaction time may vary depending on the amount of the reagent employed, the type of the solvent and the reaction temperature, it is usually about 10 minutes to about 10 hours, preferably about 30 minutes to about 3 hours. While a product still in a solution or as a crude product may be used in the next reaction, it can be isolated from a reaction mixture by an ordinary method, and can readily be purified by a separating procedure such as recrystallization, distillation, chromatography, etc.

Page 97, paragraph 3 (AMENDED)

Compound (XXIII) is obtained by alkylating the hydroxy **[groupl]** group **[in]** **of the** phenol in Compound (XXII) selectively using an alkylating agent represented by RgL. Rg denotes a **[C1-6]** C_{1-6} alkyl (e.g., methyl, ethyl, etc.), and the "leaving group" represented by L is similar to those described above.

Page 99, paragraph 3 (AMENDED)

Compound (XXIV) is obtained by converting the hydroxy **[groupl]** group in Compound (XXIII) into a halogen using a halogenating reagent.

Page 114, paragraph 5 (AMENDED)

When a starting compound has as its substituent amino, carboxyl or hydroxy **[group]** group in each reaction described above, such group may be subjected to an introduction of a protective group employed conventionally in peptide chemistry, and the protective group is removed if necessary after the **[reactiinto]** **reaction to** yield the desired compound.

Page 117, paragraph 11 (AMENDED)

Examples of the "aniline" described above include **[be]** N,N-diethylaniline, N,N-dimethylaniline, etc.

Page 119, paragraph 1 (AMENDED)

A prodrug of Compound (I) is a compound capable of being converted into Compound (I) as a result of a reaction with an enzyme, gastric acid, etc. under in vivo physiological conditions, i.e., a compound subjected to enzymatic oxidation, reduction, hydrolysis, etc. to change into Compound (I) or a compound hydrolyzed by **[a]** gastric acid to change into Compound (I). The prodrug of Compound (I) may for example be a compound resulting from acylation, alkylation or phosphorylation of amino group of Compound (I) (for example, a compound resulting from eicosanoylation, alanylation, pentylaminocarbonylation, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonylation, tetrahydrofuranylation, pyrrolidylmethylation, pivaloyloxymethylation or tert-butylation of amino group of Compound (I), etc.); a compound resulting from acylation, alkylation, phosphorylation or boration of hydroxy **[groupl]** group of Compound (I) (for example, a compound resulting from acetylation, palmitoylation, propanoylation, pivaloylation, succinylation, fumarylation, alanylation or dimethylaminomethylcarbonylation of hydroxy **[groupl]** group of Compound (I), etc.; a compound resulting from an esterification or an amidation of carboxyl group of Compound (I)

(for example, a compound resulting from ethyl esterification, phenyl esterification, carboxymethyl esterification, dimethylaminomethyl esterification, pivaloyloxymethyl esterification, ethoxycarbonyloxyethyl esterification, phthalidyl esterification, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl esterification, cyclohexyloxycarbonylethyl esterification and methylamidation of a carboxyl group of Compound (I), etc.) and the like. Any of these compounds can be produced from Compound (I) by a per se known method.

Page 120, paragraph 4 (AMENDED)

Compound (I) or (I') of the present invention exhibits a lipid peroxidation inhibitory activity based on an excellent antioxidative effect in a mammal (for example, mouse, rat, hamster, rabbit, cat, dog, cattle, sheep, monkey, human and the like), is effective in **[a]** prophylaxis and/or **[a]** therapy against a central nerve system disease or failure such as, for example, an ischemic central nerve disease (e.g., cerebral infarction, cerebral hemorrhage, cerebral edema), a central nerve damage (e.g., cranial trauma, spinal damage, whiplash), a neurodegenerative disease (e.g., Alzheimer's disease, **[Perkinson's]** **Parkinson's** disease, Huntington's chorea, amyotrophic lateral sclerosis), a vascular dementia (e.g., multi-infarct dementia, Binswanger's disease), **[maniac]** **manic**-depressive, melancholia, schizophrenia, chronic pain, trigeminal neuralgia, migraine, a circulatory system disease or failure such as, for example, an ischemic heart disease (e.g., cardiac infarction, angina **[pectris]** **pectoris**), arterial sclerosis, post-PCTA arterial restenosis, a lower urinary tract disease or failure (e.g., dysuria, urinary incontinence) and a diabetic neurosis, and is employed **[for]** **as** a prophylactic and therapeutic agent against any of these disorders listed above.

Page 123, paragraph 5 (AMENDED)

Examples of the binder include crystalline cellulose, sugar, D-mannitol, dextrin, **[hydroxy groupppropyl]** **hydroxypropyl** cellulose, **[hydroxy groupppropyl]** **hydroxypropyl** methylcellulose, polyvinyl pyrrolidone, starch, sucrose, gelatin, methyl cellulose, sodium carboxymethyl cellulose and the like.

Page 124, paragraph 2 (AMENDED)

Examples of the disintegrant include starch, carboxymethyl cellulose, potassium carboxymethyl cellulose, sodium croscarmellose, sodium carboxymethyl starch, **[L-hydroxy groupppropyl]** **L-hydroxypropyl** cellulose and the like.

Page 124, paragraph 5 (AMENDED)

Examples of the suspending agent include surfactants such as stearyl triethanolamine, sodium lauryl sulfate, lauryl aminopropionic acid, lecithin, benzalkonium chloride, benzethonium chloride, glycerin monostearate, etc.; hydrophilic polymers such as polyinyl alcohol, polyvinyl pyrrolidone, sodium carboxymethyl cellulose, methyl cellulose, **[hydroxy groupmethyl]** **hydroxymethyl** cellulose, **[hydroxy groupethyl]** **hydroxyethyl** cellulose, **[hydroxy groupppropyl]** **hydroxypropyl** cellulose, etc., and the like.

Page 130, paragraph 2 (AMENDED)

To a solution of 2,3-dihydro-2,2,4,7-tetramethyl-5H-indol-5-one (7.36 g, 38.9 mmol) in ethyl acetate (100 ml) was added a solution of sodium hydrosulfite (14.9 g, 85.6 mmol) in water

(50 ml) and shaken. The aqueous layer was separated, and the organic layer was washed with water and saturated brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was recrystallized from ethanol-hexane to obtain 6.17 g of the title compound.

Yield: 83%.

Melting point: 186 - 187°C.

^{1}H-NMR (DMSO-d_6) δ 1.21 (6H, s), 1.91 (6H, s), 2.61 (2H, s), 4.39 (1H, s), 6.22 (1H, s), 8.05 (1H, s).

Reference Example 6

2,3-Dihydro-5- hydroxy **[group]** -2,2,4,7-tetramethyl-1H-indole-1-carbaldehyde

Page 131, paragraph 1 (AMENDED)

Acetic anhydride (2.0 ml, 21 mmol) was added to formic acid (5 ml) and stirred at room temperature for 20 minutes. To the **[mixturwe]** **mixture** was added 2,3-dihydro-2,2,4,7-tetramethyl-1H-indol-5-ol (1.32 g, 6.90 mmol) and stirred at room temperature for 20 minutes. The reaction mixture was concentrated under reduced pressure, neutralized with saturated aqueous sodium hydrogen carbonate solution and extracted three times with ethyl acetate. The organic layers were combined, washed with water and saturated brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was dissolved in methanol (10 ml) and then 1N aqueous solution of sodium hydroxide (7 ml, 7 mmol) was added with cooling on ice. The mixture was stirred at the same temperature for 3 minutes. The reaction mixture was neutralized with 1N hydrochloric acid with cooling on ice, and extracted three times with ethyl acetate. The organic layers were combined, washed with water and saturated brine,

dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was recrystallized from ethanol-hexane to obtain 1.17 g of the title compound.

Yield: 77%.

Melting point: 175 - 177°C.

^{1}H-NMR ($CDCl_3$) δ 1.53, 1.66 (6H, s), 2.09 (3H, s), 2.25, 2.32 (3H, s), 2.82, 2.89 (2H, s), 5.00-6.20 (1H, br), 6.49 (1H, s), 8.32, 8.99 (1H, s).

Reference Example 7

2,3-Dihydro-2,2,4,7-tetramethyl-5-[(2-methyl-2-propenyl)oxy]-1H-indole-1-carbaldehyde

Page 132, paragraph 2 (AMENDED)

To a solution of 2,3-dihydro-5-hydroxy **[group]** -2,2,4,7-tetramethyl-1H-indole-1-carbaldehyde (2.29 g, 10.4 mmol) in DMF (15 ml) was added 60% dispersion of sodium hydride in oil (0.42 g, 12 mmol) with cooling on ice and stirred under nitrogen atmosphere at the same temperature for 5 minutes. To the resulting mixture was added 3-chloro-2-methyl-1-propene (1.3 ml, 13 mmol) and stirred at room temperature for 30 minutes and at 60°C for 15 minutes. The reaction mixture was poured into **[an]** a saturated aqueous solution of ammonium chloride, and extracted three times with ethyl acetate. The organic layers were combined, washed with water and saturated brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was recrystallized from diisopropyl ether-hexane to obtain 1.95 g of the title compound.

Yield: 69%.

Melting point: 83 - 95°C.

^{1}H-NMR ($CDCl_3$) δ 1.53, 1.65 (6H, s), 1.84 (3H, s), 2.10 (3H, s), 2.29, 2.37 (3H, s), 2.82, 2.89 (2H, s), 4.39 (2H, s), 4.98 (1H, s), 5.11 (1H, s), 6.46, 6.51 (1H, s), 8.34, 9.02 (1H, s).

Reference Example 8

2,3-Dihydro-5-hydroxy **[group]** -2,2,4,7-tetramethyl-6-(2-methyl-2-propenyl)-1H-indole-1-carbaldehyde

Page 133, paragraph 3 (AMENDED)

To a suspension of ethyl 4-[methyl(**[phenylamno]** **phenylamino**)thioxomethyl]amino]-1-piperidine carboxylate (4.02 g, 12.5 mmol) in carbon tetrachloride (25 ml) was added dropwise a solution of bromine (2.00 g, 12.5 mmol) in carbon tetrachloride (10 ml) and the mixture was stirred at room temperature for 30 minutes and heated under reflux for 1 hour. The **[insoluble was]** **insolubles were** isolated by filtration and washed with hexane. The **[insoluble was]** **insolubles were** dissolved in 48% hydrobromic acid (40 ml) and heated under reflux for 2 hours. The reaction mixture was cooled to 0°C, neutralized with 25% aqueous ammonia, and extracted twice with ethyl acetate. The organic layers were combined, washed with water and saturated brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was combined with diisopropyl ether and the **[insoluble was]** **insolubles were** removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was dissolved in methanol, combined with a 10% hydrogen chloride methanol solution (11 ml), and concentrated under reduced pressure. The residue was recrystallized from methanol-diisopropyl ether to obtain 2.53 g of the title compound.

Yield: 71%.

Melting point: 287 - 289°C.

^{1}H-NMR (DMSO-d_6) δ 1.80-2.00 (2H, m), 2.00-2.29 (2H, m), 2.91-3.26 (2H, m), 3.04 (3H, s), 3.28-3.47 (2H, m), 4.36-4.58 (1H, m), 7.04-7.17 (1H, m), 7.26-7.37 (1H, m), 7.50 (1H, d, J = 8.0 Hz), 7.81 (1H, d, J = 8.0 Hz), 9.11 (2H, br s).

Reference Example 10

2,5-Dimethoxy-1,4-dimethylbenzene

Page 139, paragraph 2 (AMENDED)

To a solution of 2,5-dimethoxy-3,6-dimethylbenzene ethanamine (22.0 g, 105 mmol) in acetonitrile (100 ml) was added dropwise a solution of cerium diammonium nitrate (120.9 g, 220 mmol) in acetonitrile (100 ml) and water (200 ml) with cooling on ice over 20 minutes. After stirring at room temperature for 1 hour, the reaction mixture was poured into a mixture of a solution of sodium hydrogen carbonate (138 g, 1640 mmol) in water (400 ml) and ethyl acetate (400 ml) and stirred at the same temperature for 30 minutes. After removing of insolubles by filtration, the organic layer was separated. The aqueous layer was extracted with ethyl acetate and the organic layers were combined. The combined organic layers were washed with saturated brine, and then treated with a solution of 80% sodium hydrosulfite (48 g, 220 mmol) in water (400 ml). The mixture was made basic using a saturated aqueous solution of sodium hydrogen carbonate, and then extracted with ethyl acetate. The extract was washed with saturated brine, dried over sodium sulfate, purified by silica gel chromatography with a small amount of silica gel and eluted with ethyl acetate. The solvent was removed under reduced pressure, and the resultant oil was crystallized from diethyl ether to obtain 14.4 g of the title compound.

Yield: 84%.

Melting point: 155 - 158°C.

^{1}H-NMR ($CDCl_3$) δ 2.05 (3H, s), 2.10 (3H, s), 2.94 (2H, t, J = 7.4 Hz), 3.05 (1H, br), 3.53 (2H, t, J = 7.4 Hz), 6.39 (1H, s), 7.40 (1H, br).

Reference Example 15

2,3-Dihydro-5-hydroxy **[group]** -4,7-dimethyl-1H-indole-1-carbaldehyde

Page 141, paragraph 2 (AMENDED)

2,3-Dihydro-5-hydroxy **[group]** -4,7-dimethyl-1H-indole-1-carbaldehyde (5.74 g, 30 mmol) was dissolved in N,N-dimethylformamide (100 ml) and to the solution were added potassium carbonate (8.29 g, 60 mmol), potassium iodide (0.50 g, 3 mmol) and 3-chloro-2-methyl-1-propene (4.41 ml, 45 mmol). The mixture was stirred at 80°C for 3 hours. The reaction mixture was poured into cold water (300 ml), and extracted with ethyl acetate. The extract was washed with saturated brine and dried over sodium sulfate, and then the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 6 : 1) to obtain 6.00 g of the title compound.

Yield: 82%.

^{1}H-NMR ($CDCl_3$) δ 1.85 (3H, s), 2.14 (3H, s), 2.39 (3H, s), 2,99 (2H, t, J = 8.0 Hz), 4.11 (2H, t, J = 8.0 Hz), 4.40 (2H, s), 4.99 (1H, s), 5,11 (1H,s), 6.48 (1H, s), 8.89 (1H, s).

Reference Example 17

2,3-Dihydro-5-hydroxy **[group]** -4,7-dimethyl-6-(2-methyl-2-propenyl)-1H-indole-1-carbaldehyde

Page 144, paragraph 2 (AMENDED)

To a solution of 2-(tert-butyl)-4-nitroso-5-methylphenol (47.0 g, 243 mmol) in ethanol (500 ml) was slowly added dropwise hydrazine hydrate (29.5 ml, 608 mmol) at 0°C. After completing the dropwise addition, the mixture was stirred at room temperature for 16 hours, and the solvent was removed under reduced pressure. The residue was combined with water (500 ml), and the crystals were filtered. The crystals were dissolved in ethyl acetate, washed with saturated brine, dried over sodium sulfate and purified by silica gel column chromatography on a small amount of silica gel which was eluted with ethyl acetate. After the solvent was removed under reduced pressure, the residue was suspended in hexane and the crystals were collected by **[filtratiinto]** **filtration to** obtain 39.3 g of the title compound.

Yield: 90%.

Melting point: 191 - 192°C.

^{1}H-NMR ($CDCl_3$) δ 1.37 (9H, s), 2.07 (3H, s), 3.25 (2H, br), 6.52 (1H, s), 6.60 (1H, s), 7.35 (1H, br).

Reference Example 20

N-[5-(tert-Butyl)-4-hydroxy **[group]** -2-methylphenyl]formamide

Page 145, paragraph 3 (AMENDED)

According to the same manner as that of Reference Example 16, 25.5 g of the title compound was obtained using N-[5-(tert-butyl)-4-hydroxy **[group]** -2-methylphenyl]formamide (35.2 g, 0.17 mol)

Yield: 57%.

Melting point: 108 - 109°C.

Reference Example 22

N-[5-(tert-Butyl)-4-hydroxy **[group]** -2-methyl-3-(2-methyl-2-propenyl)phenyl]formamide

Page 145, paragraph 4 (AMENDED)

According to the same manner as that of Reference Example 17, 20.9 g of the title compound was obtained using N-[5-(tert-butyl)-2-methyl-4-(2-methyl-2-propenyloxy)phenyl]formamide (25.4 g, 97.2 mmol).

Yield: 82%.

Melting point: 153 - 154°C.

Reference Example 23

5-Amino-7-(tert-butyl)-2,3-dihydro-2,2,4-trimethyl-1- **[benzofurane]** **benzofuran**

Page 146, paragraph 2 (AMENDED)

To a solution of N-[5-(tert-butyl)-4-hydroxy **[group]** -2-methyl-3-(2-methyl-2-propenyl)phenyl]formamide (10.45 g, 40 mmol) in methanol (100 ml) was added concentrated hydrochloric acid (40 ml) and the mixture was heated under reflux for 3 hours under argon atmosphere. After cooling to 0°C, the mixture was made weakly basic using 12N sodium hydroxide, and extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over sodium sulfate, and then the solvent was removed under reduced pressure. The residue was purified by a column chromatography on a silica gel (hexane : ethyl acetate = 1 : 1) and crystallized from hexane to obtain 6.28 g of the title compound.

Yield: 67%.

Melting point: 115 - 116°C.

^{1}H-NMR ($CDCl_3$) δ 1.31 (9H, s), 1.44 (6H, s,), 2.02 (3H, s), 2.87 (2H, s), 2.95 (2H, br), 6.47 (1H, s).

Reference Example 24

tert-butyl N-[7-(tert-butyl)-2,3-dihydro-2,2,4-trimethyl-1-benzofuran-5-yl]carbamate

Page 146, paragraph 3 (AMENDED)

5-Amino-7-(tert-butyl)-2,3-dihydro-2,2,4-trimethyl-1- **[benzofurane]** **benzofuran** (6.30 g, 27 mmol) was dissolved in THF (63 ml) and then triethylamine (5.65 ml, 40.5 mmol) was added. After cooling to 0°C, di-tert-butyl dicarbonate (6.48 g, 29.7 mmol) was added to the solution, and the mixture was stirred for 3 hours at room temperature. The reaction mixture was poured into **[a]** cold water (100 ml), and extracted with diethyl ether. The organic layer was washed with saturated brine, dried over sodium sulfate and purified by silica gel column chromatography on a small amount of silica gel which was eluted with hexane : ethyl acetate (7 : 3). The resultant oil was the title compound (7.30 g).

Yield: 81%.

Melting point: 124 - 126°C.

^{1}H-NMR ($CDCl_3$) δ 1.31 (9H, s), 1.45 (6H, s), 1.50 (9H s), 2.07 (3H, s), 2.88 (2H, s), 5.97 (1H, br), 7.06 (1H, s).

Reference Example 25

7-(tert-Butyl)-2,3-dihydro-5-(2-methyl-2-propenyl)amino-2,2,4-trimethyl-1- **[benzofurane]** **benzofuran**

Page 149, paragraph 3 (AMENDED)

To a solution of 1,4-dimethoxy-2,5-dimethyl-3-(2-nitro-1-propenyl)benzene (5.0 g, 19.9 mmol) in tetrahydrofuran (100 ml) was added lithium aluminum hydride (4.0 g, 105.4 mmol) with cooling on ice, and the reaction mixture was heated under reflux for 6 hours. To the

reaction mixture was added HIFLO-SUPERCEL (trade name) (5 g), and then **water was** added dropwise **[water]** (1.5 ml) with cooling on ice. The resultant mixture was suspended in ethyl acetate, filtered and concentrated under reduced pressure to obtain 4.2 g of the desired product as an oil.

Yield: 95%.

^{1}H-NMR ($CDCl_3$) δ 1.12 (3H, d, J = 6.4 Hz), 1.50 (2H, br s), 2.15 (3H, s), 2.29(3H, s), 2.67 (1H, dd, J = 13.2 and 7.6 Hz), 2.70 (1H, dd, J = 13.2, 5.8 Hz), 3.11 (1H, m), 3.65 (3H, s), 3.78 (3H, s), 6.56 (1H, s).

Reference Example 28

2,3-Dihydro-5-hydroxy **[group]** -2,4,7-trimethyl-1H-indole

Page 150, paragraph 2 (AMENDED)

To the solution of 1-(2,5-dimethoxy-3,6-dimethylphenyl)-2-propanamine (2.2 g, 9.4 mmol) in acetonitrile (10 ml) was added dropwise a solution of cerium (IV) diammonium nitrate (10.0 g, 18.2 mmol) in acetonitrile (20 ml) and water (20 ml) with cooling on ice, and stirred at room temperature for 2 hours. The reaction mixture was diluted with water, neutralized with sodium hydrogen **[carboante]** **carbonate**, and extracted three times with ethyl acetate. The organic layers were combined, washed with water and saturated brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure to obtain a solid. The solid was dissolved in ethyl acetate, combined with an aqueous solution of sodium hydrosulfite and shaken to precipitate a solid, which was collected by **[a filtratiinto]** **filtration to** obtain 1.2 g of the title compound.

Yield: 68%.

Melting point: 196 - 197°C.

Reference Example 29

1-Acetyl-2,3-dihydro-5-hydroxy **[group]** -2,4,7-trimethyl-1H-indole

Page 151, paragraph 2 (AMENDED)

To a solution of 2,3-dihydro-5-hydroxy **[group]** -2,4,7-trimethyl-1H-indole (1.0 g, 5.7 mmol) in pyridine (2.6 ml) was added acetic anhydride (1.7 ml, 16.6 mmol), and stirred at room temperature for 3 hours. Ice was added to the reaction mixture and the product was extracted with ethyl acetate. The extract was washed with water, dried and concentrated, and the residue was dissolved in methanol (30 ml). To the solution was added a solution of potassium carbonate (1.0 g, 7.2 mmol) in water (15 ml), and the reaction mixture was stirred at room temperature for 30 minutes. The reaction mixture was neutralized with 1N hydrochloric acid, and the product was extracted with ethyl acetate. The extract was washed with water and saturated brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate-isopropyl ether to obtain 0.89 g of the title compound.

Yield: 76%.

Melting point: 156 - 158°C.

Reference Example 30

1-Acetyl-2,3-dihydro-2,4,7-trimethyl-5-[(2-methyl-2-propenyl)oxy]-1H-indole

Page 152, paragraph 2 (AMENDED)

A suspension of 1-acetyl-2,3-dihydro-5-hydroxy **[group]** -2,4,7-trimethyl-1H-indole (3.3 g, 16.1 mmol), 3-chloro-2-methyl-1-propene (2.6 g, 28.7 mmol) and potassium carbonate (3.5 g, 25.3 mmol) in dimethylformamide (25 ml) was stirred for 20 hours at 80°C under nitrogen atmosphere. The reaction mixture was combined with water, and extracted twice with ethyl

acetate. The organic layers were combined, washed with water and saturated brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 3 : 1) to obtain 3.8 g of the title compound.

Yield: 91%.

Oil.

^{1}H-NMR ($CDCl_3$) δ 1.23 (3H, d, J = 6.4 Hz), 1.84 (3H, s), 2.11(3H, s), 2.21 (6H, s), 2.42 (1H, d, J = 15.6 Hz), 3.25 (1H, dd, J = 15.6, 7.8 Hz), 4.38 (2H, s), 4.60 (1H, m), 4.97 (1H, m), 5.11 (1H, m), 6.51 (1H, s).

Reference Example 31

1-Acetyl-2,3-dihydro-5-hydroxy **[group]** -2,4,7-trimethyl-6-(2-methyl-2-propenyl)-1H-indole

Page 153, paragraph 1 (AMENDED)

A solution of 1-acetyl-2,3-dihydro-2,4,7-trimethyl-5-[(2-methyl-2-propenyl)oxy]-1H-indole (3.8 g, 14.7 mmol) in N,N-diethylaniline (30 ml) was stirred for 2 hours at 200°C under nitrogen atmosphere. The reaction mixture was diluted with diethyl ether, and washed with 1N hydrochloric acid, water and saturated brine. The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure to obtain 3.5 g of the title compound as an oil.

Yield: 92%.

^{1}H-NMR ($CDCl_3$) δ 1.23 (3H, d, J = 7.0 Hz), 1.80 (3H, s), 2.08 (3H, s), 2.11 (6H, s), 2.20 (2H, m), 2.40 (1H, d, J = 15.8 Hz), 3.25 (1H, dd, J = 15.8, 7.8 Hz), 3.38 (2H, s), 4.60 (1H, m), 4.68 (1H, m), 4.86 (1H, m), 5.07 (1H, s).

Reference Example 32

8-Methyl-5-(1-methylethyl)-2-phenyl-4H-1,3,2- **[benzodioxaborine]** **benzodioxaborin**

Page 153, paragraph 2 (AMENDED)

Isothymol (46 ml, 0.3 mol), benzeneboric acid (38.4 g, 0.315 mol) and paraformaldehyde (purity:75%, 14.4 g, 0.36 mol) were suspended in toluene (500 ml), and to this was added propionic acid (2.23 ml, 0.03 mol). The mixture was heated under reflux for 1.5 hours with **[removing]** **removal of** the generated water using a **[Deen]** **Dean** -Stark trap. Paraformaldehyde (purity: 75%, 14.4 g, 0.36 mol) was added again, and the mixture was heated under reflux for further 1.5 hours. The reaction mixture was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (ethyl acetate : hexane = 1 : 9) to obtain 72.1 g of the title compound as an oil.

Yield: 90%.

^{1}H-NMR ($CDCl_3$) δ 1.21 (6H, d, J = 6.6 Hz), 2.37 (3H, s), 2.70-2.86 (1H, m), 5.29 (2H, s), 6.90 (1H, d, J = 8.1 Hz), 7.09 (1H, d, J = 8.1 Hz), 7.37-7.53 (3H, m), 7.96-8.01 (2H, m).

Reference Example 33

2- **[Hydroxy groupmethyl]** **Hydroxymethyl** -6-methyl-3-(1-methylethyl)phenol

Page 154, paragraph 2 (AMENDED)

In a solution of 8-methyl-5-(1-methylethyl)-2-phenyl-4H-1,3,2- **[benzodioxaborine]** **benzodioxaborin** (72.1 g, 0.27 mol) in toluene (500 ml) was added diethanolamine (259 ml, 2.7 mol), and stirred for 16 hours at 100°C. The reaction mixture was concentrated under reduced pressure, and the residue was poured into cooled 3N hydrochloric acid (1000 ml), and extracted with ethyl acetate. The extract was washed with saturated brine, dried over sodium sulfate, and

concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate : hexane = 1 : 4) to obtain 37.4 g of the title compound as an oil.

Yield: 77%.

^{1}H-NMR ($CDCl_3$) δ 1.20 (6H, d, J = 6.6 Hz), 2.21 (3H, s), 2.95-3.13 (1H, m), 4.94 (2H, s), 5.18 (1H, br), 6.75 (1H, d, J = 8.0 Hz), 7.05 (1H, d, J = 8.0 Hz).

Reference Example 34

3-Methyl-6-(1-methylethyl)-2-methoxybenzyl alcohol

Page 155, paragraph 2 (AMENDED)

2- **[Hydroxy groupmethyl]** **hydroxymethyl** -6-methyl-3-(1-methylethyl)phenol (37.3 g, 207 mmol) was dissolved in THF (350 ml), and then potassium tert-butoxide (22.1 g, 197 mmol) was added. To the mixture was added methyl iodide (19.7 ml, 311 mmol) at 0°C, and the mixture was stirred at room temperature for 16 hours. The reaction mixture was combined with water, made acidic with 1N hydrochloric acid, and extracted with ethyl acetate. The extract was washed with saturated brine, dried over sodium sulfate and purified by column chromatography on a small amount of silica gel which was eluted with ethyl acetate. The solvent was concentrated under reduced pressure, and the residue was crystallized from hexane to obtain 21.7 g of the title compound.

Yield: 54%.

Melting point: 100 - 101°C.

^{1}H-NMR ($CDCl_3$) δ 1.24 (6H, d, J = 6.6 Hz), 2.11 (1H, t, J = 6.2 Hz), 2.28 (3H, s), 3.18-3.36 (1H, m), 3.81 (3H, s), 4.78 (2H, d, J = 6.2 Hz), 7.01 (1H, d, J = 8.0 Hz), 7.14 (1H, d, J = 8.0 Hz).

Reference Example 35

3-Methyl-6-(1-methylethyl)-2-methoxybenzyl bromide

Page 160, paragraph 2 (AMENDED)

2,5-Dimethylnitrobenzene (46.8 ml, 0.35 mol) was dissolved in sulfuric acid (47.1 ml)/methanol (650 ml) and then 5% **[iridium]** **palladium** on carbon (50% hydrate, 0.35 g) was added. The mixture was allowed to react for 3 hours under hydrogen atmosphere at the pressure of 5 atms at 40°C. After cooling, the catalyst was removed, and methanol was removed under reduced pressure. The residue was poured into a 25% aqueous ammonia **solution** with cooling on ice, and extracted with toluene. The extract was washed with 5% sodium hydrosulfite, dried over sodium sulfate and purified by column chromatography on a small amount of silica gel (toluene : ethyl acetate = 1 : 1). The solvent was removed under reduced pressure and **[a]** crystallization from hexane yielded 35.0 g of the title compound.

Yield: 66%.

Melting point: 75 - 76°C.

^{1}H-NMR ($CDCl_3$) δ 2.15 (6H, s), 3.29 (2H, br), 3.76 (3H, s), 6.51 (1H, s), 6.58 (1H, s).

Reference Example 41

4,7-Dimethyl-5-methoxy-3-(methylthio)-1,3-dihydro-2H-indol-2-one

Page 160, paragraph 3 (AMENDED)

To a solution of methyl (methylthio)acetate (14.8 ml, 115 mmol) in dichloromethane (400 ml) was added sulfuryl chloride (9.64 ml, 120 mmol) at -78°C and stirred for 15 minutes. To the mixture was added dropwise a solution of 4-methoxy-2,5-dimethylaniline (15.1 g, 100 mmol) and proton sponge (22.5 g, 105 mmol) in dichloromethane (100 ml) over 1 hour and the mixture was stirred at the same temperature for 1 hour. Then, triethylamine (15.3 ml, 110

mmol) was added, and the mixture was allowed to warm to room temperature slowly. After stirring at room temperature for 1 hour, water was added and the precipitated **[crystal was]** **crystals were** collected by **[a]** filtration and washed with dichloromethane and water to obtain 18.3 g of the title compound.

Yield: 77%.

Melting point: 226 - 227°C.

^{1}H-NMR ($CDCl_3$) δ 2.04 (3H, s), 2.24 (3H, s), 2.26 (3H, s), 3.79 (3H, s), 4.20 (1H, s), 6.55 (1H, s), 8.40 (1H, brs).

Reference Example 42

4,7-Dimethyl-5-methoxy-1,3-dihydro-2H-indol-2-one

Page 166, paragraph 1 (AMENDED)

2,3-Dihydro-5-hydroxy **[group]** -4,7-dimethyl-6-(2-methyl-2-propenyl)-1H-indole-1-carbaldehyde (491 mg, 2.0 mmol) was dissolved in methanol (6 ml). To the solution was added concentrated hydrochloric acid (6 ml) and stirred for 3 hours with heating under reflux. The reaction mixture was cooled to 0°C, made weakly basic with 12N sodium hydroxide, and extracted with ethyl acetate. The extract was washed with saturated brine and dried over sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 2 : 1) and crystallized from hexane to obtain 330 mg of the title compound.

Yield: 76%.

Melting point: 105 - 107°C.

^{1}H-NMR ($CDCl_3$) δ 1.45 (6H, s), 2.01 (3H, s), 2.08 (3H, s), 2.45 (1H, br), 2.89 (2H, s), 2.93 (2H, t, J = 8.3 Hz), 3.55 (2H, t, J = 8.3 Hz).

Example 2

5-Acetyl-(2,2,4,6,8-pentamethyl-3,5,6,7-tetrahydro-2H-furo[2,3-f]indole

Page 166, paragraph 2 (AMENDED)

To a solution of 1-acetyl-2,3-dihydro-5-hydroxy **[group]** -2,4,7-trimethyl-6-(2-methyl-2-propenyl)-1H-indole (3.5 g, 13.5 mmol) in methanol (30 ml) was added concentrated hydrochloric acid (10 ml) and heated under reflux for 30 minutes under nitrogen atmosphere. The reaction mixture was diluted with water, and the product was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate-isopropyl ether to obtain 2.6 g of the title compound.

Yield: 74%.

Melting point: 154 - 155°C.

Example 3

2,2,4,6,8-Pentamethyl-3,5,6,7-tetrahydro-2H-furo[2,3-f]indole

Page 168, paragraph 2 (AMENDED)

7-tert-butyl-5-(2-methyl-2-propenyl)amino-2,2,4-trimethyl-2,3- **[dihydrobenzofurane]** **dihydrobenzofuran** (5.75 g, 20 mmol) was dissolved in xylene (60 ml), combined with zinc chloride (6.82 g, 50 mmol) and heated under reflux for 32 hours under argon atmosphere. The reaction mixture was cooled, and combined **with** a saturated aqueous solution of sodium acetate (100 ml), and the mixture was extracted with ethyl acetate. The extract was washed with 1N sodium hydroxide and saturated brine and dried over sodium sulfate and the solvent was

removed under reduced pressure. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 4 : 1) to obtain an oil, which was treated with a 4N hydrochloric acid ethyl acetate solution and crystallized from ethyl acetate to obtain 2.56 g of the title compound.

Yield: 40%.

Melting point: 293 - 296°C.

NMR data of a free base is shown below.

^{1}H-NMR ($CDCl_3$) δ 1.30 (6H, s), 1.39 (9H, s), 1.42 (6H, s), 1.95 (3H, s), 2.52 (1H, br), 2.81 (2H, s), 3.08 (2H, s).

Example 5

3,5,6,7-Tetrahydro-2- **[hydroxy groupmethyl]** **hydroxymethyl** -2,4,8-trimethyl-2H-furo[2,3-f]indole-5-carbaldehyde

Page 169, paragraph 2 (AMENDED)

To a solution of 2,3-dihydro-5-hydroxy **[group]** -4,7-dimethyl-6-(2-methyl-2-propenyl)-1H-indole-1-carbaldehyde (491 mg, 2.0 mmol) in dichloromethane (5 ml) and saturated sodium hydrogen carbonate (2.5 ml) solution was added m-chloroperbenzoic acid (863 mg, 5 mmol) with cooling on ice and stirred for 2 hours at room temperature. Dichloromethane was removed under reduced pressure, and the residue was combined **with** ethyl acetate (10 ml) and triethylamine (2 ml) and washed with water. To the organic layer was added a 10% aqueous solution of sodium hydrosulfite (10 ml) and shaken, and then the organic layer was separated. The organic layer was washed with a saturated aqueous solution of sodium hydrogen carbonate and saturated brine and dried over sodium sulfate, and then the solvent was removed under

reduced pressure. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 1 : 2) and crystallized from hexane to obtain 91 mg of the title compound.

Yield: 17%.

Melting point: 163 - 165°C.

^{1}H-NMR ($CDCl_3$) δ 1.44 (3H, s), 2.08 (3H, s), 2.26 (3H, s), 2.80-2.96 (3H, m), 3.22 (1H, d, J = 15.4 Hz), 3.65 (2H, dd, J = 11.7, 20.5 Hz), 4.11 (2H, t, J = 8.1 Hz)8.81 (1Hs).

Example 6

8-tert-Butyl-5-(4-fluorobenzoyl)-3,5,6,7-tetrahydro-2,2,4,6,6-pentamethyl-2H-furo[2,3-f]indole

Page 171, paragraph 2 (AMENDED)

2,3-Dihydro-5-hydroxy **[group]** -4,7-dimethyl-6-(2-methyl-2-propenyl)-1H-indole-1-carbaldehyde (4.17 g, 17.0 mmol) was dissolved in methanol-THF solution (34 ml, 1 : 1). To the mixture was added calcium carbonate (2.21 g, 22.1 mmol) and then trimethylammonium dichloroiodate (6.51 g, 18.7 mmol) was added. After stirring for 1 hour at room temperature, the reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was combined a 10% aqueous solution of sodium thiosulfate, and extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried over sodium sulfate, and the solvent was removed under reduced pressure. The residue was crystallized from ethyl acetate-hexane to obtain 5.52 g of the title compound.

Yield: 88%.

^{1}H-NMR ($CDCl_3$) δ 1.67 (3H, s), 2.08 (3H, s), 2.27 (3H, s), 2.93 (2H, t, J = 8.1 Hz), 2.99 (1H, d, J = 15.8 Hz), 3.26 (1H, d, J = 15.8 Hz), 3.43 (2H, s), 4.12 (2H, t, J = 8.1 Hz), 8.83 (1H, s).

Example 8

3,5,6,7-Tetrahydro-2-(iodomethyl)-2,4,8-trimethyl-2H-furo[2,3-f]indole

Page 176, paragraph 2 (AMENDED)

To a solution of 2,3-dihydro-5-hydroxy **[group]** -2,2,4,7-tetramethyl-6-(2-methyl-2-propenyl)-1H-indole-1-carbaldehyde (1.90 g, 6.95 mmol) in dichloromethane (20 ml) and methanol (10 ml) were added calcium carbonate (0.90 g, 9.0 mmol) and benzyltrimethylammonium dichloroiodate (2.66 g, 7.64 mmol), and stirred for 15 minutes at room temperature. The reaction mixture was filtered and concentrated under reduced pressure. To the residue was added a 5% aqueous solution of sodium hydrogen sulfite (15 ml), and extracted twice with ethyl acetate. The organic layers were combined, washed with saturated brine and water, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate-hexane to obtain 2.40 g of the title compound. Yield: 86%.

Melting point: 124 - 126°C.

^{1}H-NMR ($CDCl_3$) δ 1.53, 1.57 (3H, s), 1.63, 1.64 (3H, s), 1.67 (3H, s), 2.04 (3H, s), 2.14, 2.25 (3H, s), 2.78, 2.84 (2H, s), 2.99 (1H, d, J = 16.0 Hz), 3.26 (1H, d, J = 16.0 Hz), 3.43 (2H, s), 8.32, 8.96 (1H, s).

Example 13

3,5,6,7-Tetrahydro-2-(iodomethyl)-2,4,6,6,8-pentamethyl-2H-furo[2,3-f]indole

Page 177, paragraph 2 (AMENDED)

To a solution of 2,3,6,7-tetrahydro-2-(iodomethyl)-2,4,6,6,8-pentamethyl-5H-furo[2,3-f]indole-5-carbaldehyde (2.42 g, 6.06 mmol) in methanol (10 ml) was added concentrated hydrochloric acid (3 ml), and heated under reflux for 2.5 hours under nitrogen atmosphere. The reaction mixture was added dropwise to a mixture of sodium hydrogen carbonate (3.7 g, 44

mmol) with water-ethyl acetate, neutralized and extracted three times with ethyl acetate. The organic layers were combined, washed with water and saturated brine, dried over magnesium sulfate, filtered and concentrated under **[reduce]** **reduced** pressure to obtain 2.20 g of the title compound.

Yield: 98%.

An analytical sample was recrystallized from hexane.

Melting point: 100 - 104°C.

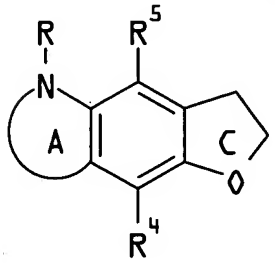
^{1}H-NMR ($CDCl_3$) δ 1.33 (6H, s), 1.64 (3H, s), 1.98 (3H, s), 2.03 (3H, s), 2.10-2.60 (1H, br), 2.76 (2H, s), 2.92 (1H, d, J = 15.9 Hz), 3.18 (1H, d, J = 15.9 Hz), 3.41 (2H, s).

Example 14

3,5,6,7-Tetrahydro-2,4,6,6,8-pentamethyl-2-[(4-phenylpiperidino)methyl]-2H-furo[2,3-f]indole

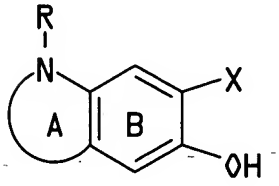
In the Claims

6. (AMENDED) The compound according to Claim 1 which is represented by the formula:



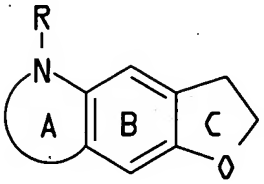
wherein R^4 and R^5 are the same or different and each denotes hydrogen atom, a halogen atom, hydroxy group **[group]**, amino group or a hydrocarbon group which may be bonded directly or via oxygen atom, nitrogen atom or sulfur atom and which may be substituted, and the other symbols are as defined in Claim 1, provided that both R^4 and R^5 are not hydrogen atoms at the same time, or a salt thereof.

18. (AMENDED) A process for preparing the compound according to Claim 1 or a salt thereof which comprises subjecting a substituent X and hydroxy group **[group]** on Ring B of a compound represented by the formula:



wherein X is an optionally substituted allyl group, and the other symbols are as defined in Claim 1 or a salt thereof to a ring-closure reaction.

19. (AMENDED) A pharmaceutical composition comprising a compound represented by the formula:



wherein Ring A is a non-aromatic 5- to 7-membered nitrogen-containing heterocyclic ring which may be further substituted, Ring B is benzene ring which is further substituted, Ring C is a dihydrofuran ring which may be further substituted and R is hydrogen atom or an acyl group, or a salt thereof or a prodrug thereof;

and a pharmaceutically acceptable carrier.

REMARKS

I. Amendments

By this amendment, claims 6, 18 and 19 have been amended; claims 20-24 and 29-32 have been cancelled.

Typographical and grammatical errors have also been corrected throughout the specification.

This amendment adds no new matter to the specification. Support for this amendment is found in the specification and claims as filed.

In particular, claims 9 and 18 have been amended to remove the redundant word "group" and claim 19 has been amended to recite pharmaceutically acceptable carriers in accordance with page 121, line 20 - page 122, line 4.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached pages are captioned "Version with Markings to Show Changes Made".

No change of inventorship is necessitated by this amendment.

II. **Conclusion**

Consideration of the claims and allowance is requested. Should the Examiner believe that a conference with Applicants' attorney would advance prosecution of this application, the Examiner is respectfully requested to call Applicants' attorney at (847) 383-3391.

Respectfully submitted,

Dated: September 4, 2002

Elaine M Ramesh

(847) 383-3391
(847) 383-3372

Elaine M. Ramesh, Ph.D., Reg. No. 43,032
Mark Chao, Ph.D., Reg. No. 37,293

Attorney for Applicants
Customer No. 23,115

Takeda Pharmaceuticals North America, Inc.
Intellectual Property Department
Suite 500, 475 Half Day Road
Lincolnshire, IL 60069 USA

Certificate of Mailing under 37 CFR 1.10

The undersigned hereby certifies that this document, along with any attachments, is being deposited in an envelope addressed to The Commissioner of Patents and Trademarks, with sufficient postage with the United States Postal Service EXPRESS MAIL Post Office to Addressee Service on this date September 4, 2002.

Express Mail Label No. EV 082675917 US

Gail L. Winokur

Printed Name: Gail L. Winokur